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Cefepime Related Neurological Complications in a Dialysis Patient: A Case Report

Diyaliz Hastasında Sefepime Bağlı Nörolojik Komplikasyonlar: Olgu Sunumu

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ABSTRACT

Cefepime, a parenteral fourth-generation cephalosporin, is used to treat multi-resistant and severe infections. However, it can induce neurotoxicity, especially in patients with renal impairment. In this case, the 30-year-old male patient, undergoing hemodialysis for chronic renal failure, presented with dysuria. Cefepime treatment was initiated following the identification of Staphylococcus aureus growth in both catheter and peripheral blood cultures. On the third day of treatment, the patient exhibited altered consciousness, impaired coordination, and dysarthric speech. Drug intoxication due to cefepime was suspected, leading to its discontinuation and early hemodialysis. The patient was then switched to piperacillin-tazobactam, and all negative neurological symptoms improved on the second day. Adjusting the maintenance dose based on renal function is important, although neurotoxicity may still occur. Clinicians should closely monitor patients with reduced renal function for changes in mental status. If cefepime toxicity is suspected, discontinuing the drug and considering dialysis may improve the patient's clinical symptoms.

Key Words: *Antimicrobial agents; Cefepime; Reduced renal function; Neurotoxicity; Confusion*

ÖZ

Diyaliz Hastasında Sefepime Bağlı Nörolojik Komplikasyonlar: Olgu Sunumu

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Sefepim, dördüncü nesil sefalosporin grubu, parenteral olarak uygulanan bir ilaç olup dirençli ve ciddi infeksiyonların tedavisinde kullanılır. Ancak özellikle renal bozukluğu olanlarda nörotoksisiteye neden olabilir. Bu makalede, kronik böbrek yetmezliği nedeniyle hemodiyaliz programına katılan 30 yaşındaki erkek hasta, dizüri şikayetiyle başvurdu. Kateter ve periferik kan kültürlerinde Staphylococcus

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aureus üremesi tespit edilmesi üzerine sefepim tedavisi başlandı. Tedavinin üçüncü gününde hastada bilinç bulanıklığı, koordinasyon bozukluğu ve dizartrik konuşma ortaya çıktı. Sefepime bağlı ilaç toksisitesi şüphesiyle ilacın kesilmesi ve erken hemodiyaliz başlanması kararı alındı. Hastanın tedavisinde daha sonra piperasilin-tazobaktama geçildi ve tüm negatif nörolojik belirtiler ikinci günde iyileşme gösterdi. Renal fonksiyona bağlı doz ayarlaması yapılsa da nörotoksisite görülebilmektedir. Azalmış renal fonksiyonu olan hastaların mental durumundaki değişiklikleri yakından takip etmek önemlidir. Sefepim toksisitesi şüphesi varsa, ilacın kesilmesi ve diyaliz başlanması ile istenmeyen etkiler düzeltilebilir.

Anahtar Kelimeler: *Antimikrobiyal ajanlar; Sefepim; Böbrek fonksiyonlarında azalma; Nörotoksisite; Konfüzyon*

INTRODUCTION

Cephalosporins have a broad spectrum of activity against gram-positive and gram-negative bacteria with excellent tissue penetration. They are suitable for treating various local and systemic infections[1]. Cefepime is a parenteral fourth-generation cephalosporin commonly used for treating multi-resistant and severe infections. It is primarily excreted by kidneys. Thus, neurotoxicity induced by cefepime is a documented adverse outcome in individuals with renal impairment. The symptoms are associated with decreased cefepime clearance due to a decline in glomerular filtration rate (GFR) and altered central nervous system penetration due to blood-brain barrier dysfunction[2]. Neurotoxicity is associated with drug overdose. Therefore, careful dose adjustment is important, especially in elderly patients and those with renal impairment[3].

This case report aims to report the neurological disturbances observed in a male patient receiving hemodialysis within two days after cefepime initiation.

CASE REPORT

A male patient in his early thirties with a history of chronic kidney disease and posterourethral valve due to vesicoureteral reflux underwent two surgical interventions. He was a regular hemodialysis patient, undergoing dialysis three times a week. The patient was admitted to the hospital on July 11th for tunneled dialysis catheter insertion. The laboratory parameters showed leukocytosis (15.84 x 10^3/µL). The C-reactive protein (CRP) level measured at 2.50 mg/dL (reference range= 0-0.8 mg/dL) and the procalcitonin level at 1.67 ng/mL (reference range= 0-0.1 ng/mL) were considered noteworthy within the context of infection. He experienced dysuria and pyuria, prompting the initiation of ceftriaxone for a suspected urinary tract infection. In the urine dipstick test, leukocyte esterase and nitrite positivity were detected, suggestive of pyuria, thus indicating a significant urinary tract infection. Microscopic examination revealed 86 leukocytes per high power field (HPF), along with a moderate growth of bacteria per HPF. These findings collectively underscore the clinical importance of the urinary tract infection. Moreover, he experienced a fever of 38.3 °C at the beginning of his hospitalization. Ceftriaxone and cefazolin treatment was considered appropriate, but ceftazidime was administered as an alternative since the medications were not available in the hospital pharmacy.

Two days after the ceftazidime treatment, *Staphylococcus aureus* growth was reported in both blood and catheter cultures. The central venous catheter was removed immediately, and the treatment was changed to cefepime due to its higher efficacy against gram-positive bacteria. Intravenous cefepime (2 g IV t.i.d. loading dose followed by 1 g once daily maintenance dose following dialysis) and teicoplanin treatment (12 mg/kg t.i.d. loading dose followed by 12 mg/kg every 72 hours) were initiated pending methicillin susceptibility results of *S. aureus* blood and catheter cultures. Concomitant medications included calcitriol, granisetrone, and sodium hydrogen carbonate. The patient had no hepatic dysfunction; his serum creatinine level was 11.59 mg/dL, and estimated glomerular filtration rate was 5.16 ml/min/1.73 m^2. On the third day of treatment, the patient exhibited altered consciousness, impaired coordination, and dysarthric speech, with a Glasgow Coma Scale (GCS) score of 9, which indicates severe impairment. The patient responded to pain

stimuli, used isolated words, and had no eye opening. A brain computed tomography scan was conducted, and no evidence of bleeding was identified upon evaluation by the neurology department. Subsequently, magnetic resonance imaging also revealed no pathological findings. Drug intoxication was considered a potential underlying cause due to neurologic complications emerging following cefepime initiation, and the drug was discontinued.

There were no considerable modifications in laboratory parameters or evident abnormalities in imaging outcomes. The Naranjo Adverse Drug Reaction Probability Scale was used to evaluate the possibility of cefepime-related blurred consciousness and lack of coordination as an adverse drug reaction. The total score on the Naranjo Scale was six and classified as "possible" (Table 1), which indicates that there is some evidence to suggest a potential association between the medication and the adverse reaction[4].

Following the emergence of neurological complications, cefepime was discontinued. The patient underwent hemodialysis two days earlier than planned and was switched to piperacillin-tazobactam. Taking into consideration the risk of recurrence of the neurological reaction associated with the cephalosporin group, piperacillin-tazobactam, an antibiotic outside the cephalosporin group and available in the hospital, was initiated. Also, teicoplanin was discontinued on its fourth dose after a lab report of methicillin-sensitive *Staphylococcus aureus*. On the second day of PIP-TAZ treatment, the GCS score improved to 15, indicating full consciousness. The patient's eyes were spontaneously open, he followed commands and provided appropriate verbal responses, indicating orientation. Piperacillin-tazobactam was discontinued after four days, as the total duration of antibiotic treatment reached ten days, and no growth was observed in the last blood cultures. Also, informed consent was obtained from the patient.

DISCUSSION

This case report emphasizes the occurrence of neurological complications in a patient with renal impairment who is currently undergoing dialysis despite appropriate cefepime dosing according to the renal function. It highlights the importance of monitoring patients closely for the potential for neurological adverse effects even when medication dosages are adjusted.

Neurotoxicity associated with beta-lactam antibiotics has been reported previously[1,3]. However, while the exact mechanism remains unclear, it is believed to involve competitive antagonism of the brain's primary inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). This inhibition could lower the neuronal threshold and cause excitation. Additionally, cephalosporins may impact GABA release from

Table 1. Naranjo Adverse Drug Reaction Probability Scale scores for the case

Naranjo Adverse Drug Reaction Probability Scale	
Questions	**Score**
Are there previous conclusive reports of this reaction?	1
Did the adverse event appear after the drug was given?	2
Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was given?	1
Did the adverse reaction reappear upon readministering the drug?	0
Were there other possible causes for the reaction?	2
Did the adverse reaction reappear upon administration of placebo?	0
Was the drug detected in the blood or other fluids in toxic concentrations?	0
Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?	0
Did the patient have a similar reaction to the drug or a related agent in the past?	0
Was the adverse event confirmed by any other objective evidence?	0
Total score	6

nerve terminals or increase the release of excitatory amino acids[1]. In this case report, the cefepime-associated neurotoxicity symptoms, such as disorientation, altered consciousness, and confusion observed, were similar to previous reports[3]. The time frame for symptom onset after drug exposure can vary, typically from one day to one month[3]. In our patient, symptoms appeared on the third day after drug exposure.

Paul et al. reported that cefepime caused significant adverse effects despite dose adjustments according to renal functions[5]. In another study of 100 patients, 15 likely cases of cefepime-induced encephalopathy were identified, with seven patients classified as definite. Four patients had their cefepime dose adjusted based on renal function, but adverse effects persisted[6].

Unfortunately, we cannot monitor cefepime serum concentrations in our hospital, but the relationship between high serum concentrations of cefepime and neurotoxicity has been reported[7]. Besides the toxic cefepime concentration threshold, various factors, including inflammation, severe sepsis, toxins, and metabolic disorders, with renal dysfunction, may collectively enhance its neurotoxic potential by affecting the blood-brain barrier[7,8].

Patients who experience unexplained neurological symptoms under cefepime treatment should be evaluated for possible drug-related adverse events as soon as possible, and the antibiotic should be discontinued. If possible, electroencephalography and serum concentration assessments may help confirm the diagnosis, but clinical judgment is more crucial. The immediate cessation of the drug and hemodialysis can be beneficial for the instant clearing of cefepime from the body[8].

In some reported cases, modifications were made to drug treatment, including the addition of anticonvulsants[1]. Since no convulsions were observed in our patient, we substituted cefepime with a non-cephalosporin antibiotic and completed the treatment.

CONCLUSION

In conclusion, cefepime treatment in patients with altered kidney function may lead to significant but reversible neurotoxicity. The maintenance dose should be adjusted according to the renal function to minimize the risk of neurotoxicity; however, neurotoxicity may still occur. In cases of reduced renal function, clinicians should be aware of the mental status changes. If cefepime toxicity is suspected, discontinuing the drug, switching to an alternative medication, and considering dialysis may help improve the patient's clinical symptoms.

CONFLICT of INTEREST

No conflict of interest declared.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: İB, TM

Analysis/Interpretation: All of authors

Data Collection or Processing: İB, TM

Writing: İB, TM

Review and Correction: EK, ÖU

Final Approval: EK, ÖU

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